(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 July 2006 (06.07.2006)

PCT

(10) International Publication Number
WO 2006/069754 A1

(51) International Patent Classification:
A61K 31/517 (2006.01)

(21) International Application Number:
PCT/EP2005/013974

(22) International Filing Date:
23 December 2005 (23.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
102004063755.5
29 December 2004 (29.12.2004) DE

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF CGRP ANTAGONISTS IN TREATMENT AND PREVENTION OF HOT FLUSHES IN PROSTATE CANCER PATIENTS

(57) Abstract: The invention relates to a method of treatment or prevention of hot flushes in men who underwent castration, e.g. due to androgen ablation treatment in prostate cancer therapy, comprising administration of an effective amount of a selected CGRP antagonist to the patient, and to the use of said active compounds for the manufacture of a pharmaceutical composition intended to be used in this method.

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Use of CGRP antagonists in treatment and prevention of hot flushes in prostate cancer patients

Technical field of the invention

The present invention relates to a method of treatment or prevention of hot flushes in men who underwent castration, e.g. due to androgen ablation treatment in prostate cancer therapy, comprising administration of an effective amount of a selected CGRP antagonist to a person in need of such treatment. The method according to the invention preferably comprises monotherapy with a single substance, but also includes combined therapy with a number of substances from the specified group of active substances.

In a second aspect, the invention relates to the use of a selected CGRP antagonist for manufacture of a pharmaceutical composition for prevention or treatment of hot flushes in men who underwent castration.

Background of the invention

Hot flushes and sweating, that is vasomotor symptoms, are reported by 43 to 77% of prostate cancer patients after medical or surgical castration, usually persisting for many years, possibly impairing quality of life (Arch. Surg. 43: 209, 1941; J. Urol. 152: 1170, 1994). Furthermore, hot flushes occur in 75% of women after menopause. In WO 01/10425 it has been proposed that the symptoms of menopausal hot flushes can be effectively prevented or their distressing effects substantially alleviated by substances which antagonise the effects of CGRP (CGRP antagonists) or inhibit or reduce the release of CGRP from sensory nerve endings (CGRP release inhibitors), this therapeutic approach being superior to hormone replacement therapy in particular because of its lack of side effects.

Although it has been already reported that plasma calcitonin gene-related peptide was increased during hot flushes in six men who underwent castration therapy, the mechanism of hot flushes in men is not well known. For instance, it is unclear up to now why some men have vasomotor symptoms whereas some do not and it was

suggested to discover more about the mechanism of these symptoms to develop new treatment alternatives (J. Urol. 166: 1720-1723, 2001).

Brief summary of the invention

There is a clear need for alternative approaches and improvement in the treatment and prevention of hot flushes in men who underwent castration.

It is therefore an object of the invention to provide a method of treatment and prevention of hot flushes in men who underwent castration, comprising administering to a patient in need of such treatment an effective amount of a selected CGRP antagonist.

A second object of the invention is the use of a selected CGRP antagonist for manufacture of a pharmaceutical composition for prevention or treatment of hot flushes in men who underwent castration.

Detailed description of the invention

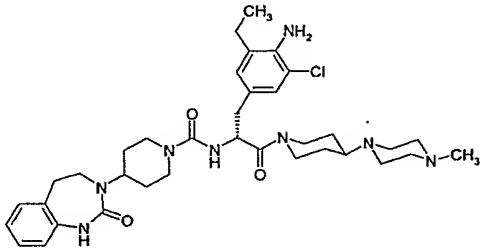
It has now been found that the symptoms of hot flushes in men who underwent castration can be effectively prevented or their distressing effects substantially alleviated by substances which antagonise the effects of CGRP (CGRP antagonists), this therapeutic approach being superior to conventional therapy.

The present invention thus relates to the use of selected CGRP antagonists for combating hot flushes in men who underwent castration, including both prevention and acute treatment. The use according to the invention preferably comprises monotherapy with a single substance, but also includes combined therapy with a number of substances from the specified groups of active substances. Moreover, the treatment according to the invention may be carried out in addition to conventional therapy.

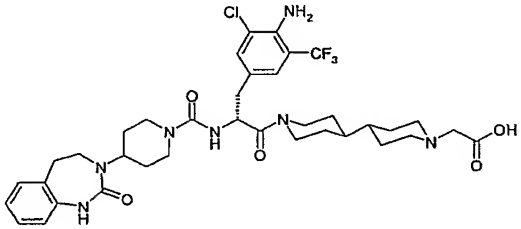
The CGRP antagonists according to the present invention which may be used for the treatment and/or prevention of hot flushes in men who underwent castration, for the

preparation of a corresponding pharmaceutical composition, are selected from the group consisting of

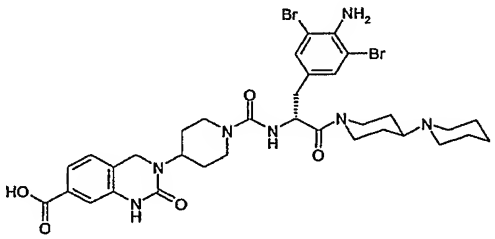
(1) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-ethyl-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl}-amide,



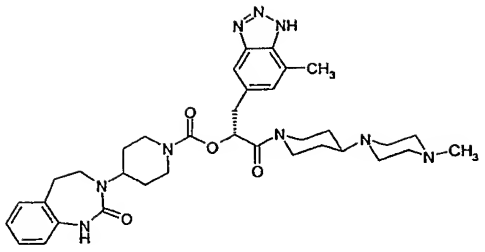
(2) [1'-((*R*)-3-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-{[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carbonyl]-amino}-propionyl)-4,4'-bipiperidinyl-1-yl]-acetic acid,



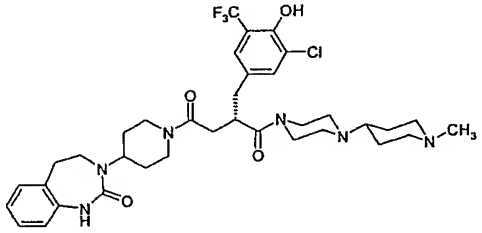
(3) 3-{1-[(*R*)-1-(4-amino-3,5-dibromo-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylcarbamoyl]-piperidine-4-yl}-2-oxo-1,2,3,4-tetrahydro-chinazolin-7-carboxylic acid,



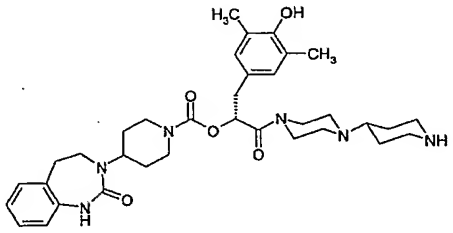
(4) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(7-methyl-1*H*-benztriazol-5-ylmethyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl ester,



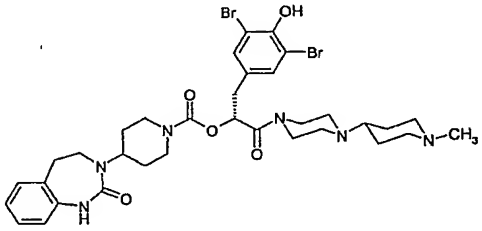
(5) (*S*)-2-(3-chloro-4-hydroxy-5-trifluoromethyl-benzyl)-1-[4-(1-methyl-piperidine-4-yl)-piperazine-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-yl]-butane-1,4-dione,



(6) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-piperidine-4-yl-piperazine-1-yl)-ethyl ester,

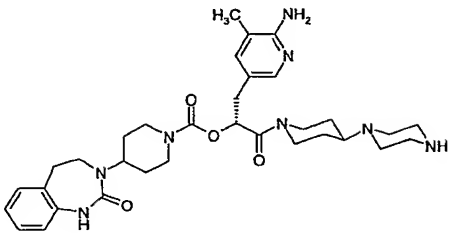


(7) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-[4-(1-methyl-piperidine-4-yl)-piperazine-1-yl]-2-oxo-ethyl ester,

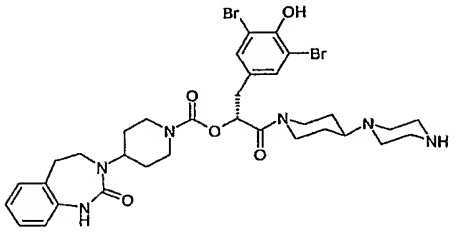


(8) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(6-amino-5-methyl-pyridine-3-ylmethyl)-2-oxo-2-(4-

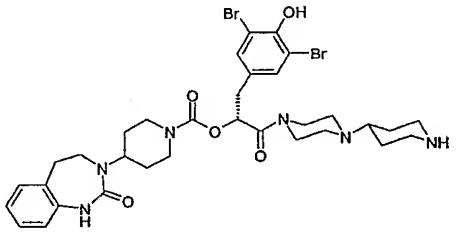
piperazine-1-yl-piperidine-1-yl)-ethyl ester,



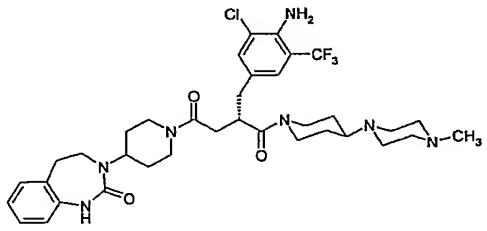
(9) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-oxo-2-(4-piperazine-1-yl-piperidine-1-yl)-ethyl ester,



(10) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-oxo-2-(4-piperidine-4-yl-piperazine-1-yl)-ethyl ester,

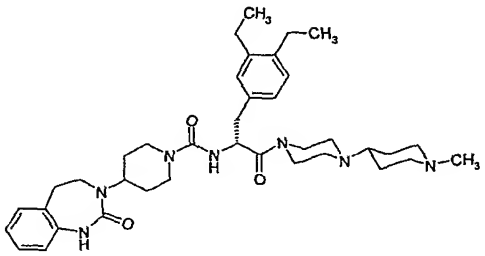


(11) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-yl]-butane-1,4-dione,

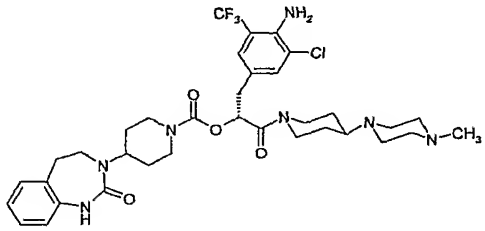


(12) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-

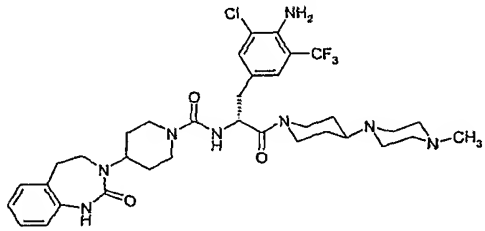
carboxylic acid {(*R*)-1-(3,4-diethyl-benzyl)-2-[4-(1-methyl-piperidine-4-yl)-piperazine-1-yl]-2-oxo-ethyl}-amide,



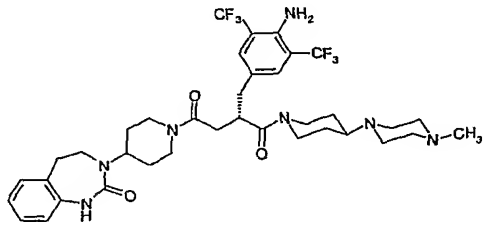
(13) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl ester,



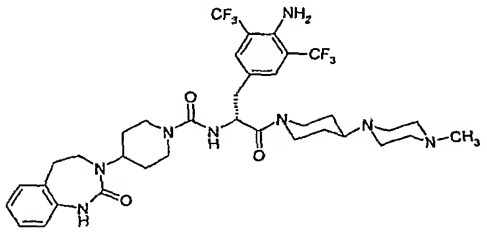
(14) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl}-amide,



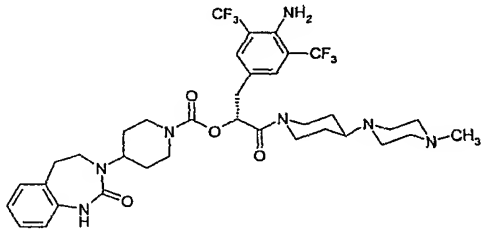
(15) ((*S*)-2-(4-amino-3,5-bis-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-yl]-butane-1,4-dione,



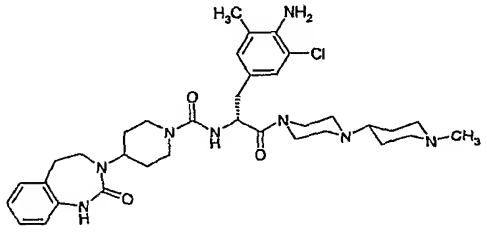
(16) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl}-amide,



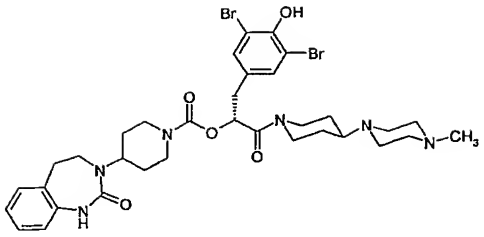
(17) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl ester,



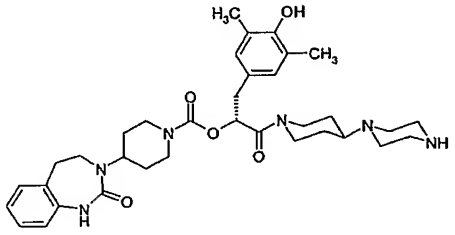
(18) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-methyl-benzyl)-2-[4-(1-methyl-piperidine-4-yl)-piperazine-1-yl]-2-oxo-ethyl}-amide,



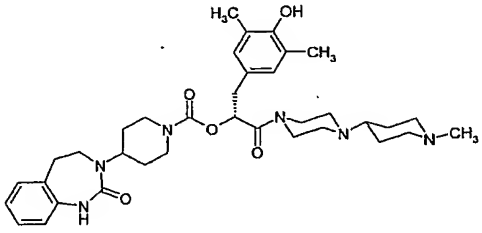
(19) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-[4-(4-methyl-piperazine-1-yl)-piperidine-1-yl]-2-oxo-ethyl ester,



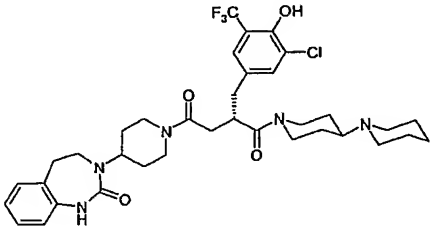
(20) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-piperazine-1-yl-piperidine-1-yl)-ethyl ester,



(21) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-[4-(1-methyl-piperidine-4-yl)-piperazine-1-yl]-2-oxo-ethyl ester,



(22) (*S*)-1-1,4'-bipiperidinyl-1'-yl-2-(3-chloro-4-hydroxy-5-trifluoromethyl-benzyl)-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzdiazepin-3-yl)-piperidine-1-yl]-butane-1,4-dione,



the physiologically acceptable salts thereof and the hydrates of the salts.

The dosage required to produce the desired effect is appropriately 0.0001 to 3 mg/kg of body weight, preferably 0.01 to 1 mg/kg of body weight, for intravenous or subcutaneous administration, 0.01 to 20 mg/kg of body weight, preferably 0.1 to 20 mg/kg of body weight, for oral administration and 0.01 to 10 mg/kg of body weight, preferably 0.1 to 10 mg/kg of body weight, by nasal route or by inhalation, 1 to 3 times a day in each case.

If the treatment with the selected CGRP antagonists is given as a supplement to conventional therapy, it is advisable to reduce the doses given above, and in this case the dosage may range from 1/5 of the lower limits specified above up to 1/1 of the upper limits specified above.

For this purpose, the selected CGRP antagonists, the physiologically acceptable salts thereof or the hydrates of said salts may be formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, metering aerosols or suppositories.

Preparations which are particularly suitable for the method of treatment or prevention according to the invention are those which contain one of the selected CGRP antagonists, a physiologically acceptable salt thereof or a hydrate of said salt.

in one of the following pharmaceutical formulations:

capsules for powder inhalation containing 1 mg of active substance,

inhalable solution for nebulisers containing 1 mg of active substance,

nasal spray containing 1 mg of active substance,

tablets containing 20 mg of active substance,

capsules containing 20 mg of active substance,

aqueous solution for nasal application containing 10 mg of active substance,

aqueous solution for nasal application containing 5 mg of active substance, or

suspension for nasal application containing 20 mg of active substance.

In the method according to the invention and in any of the formulations given the selected CGRP antagonist may also be used in form of a physiologically acceptable salt or a hydrate of said salt. Amounts are given based on the free base.

CGRP is released by sensory nerves, e.g. the trigeminal nerve which innervates part of the skin of the face. It has already been shown that stimulation of the trigeminal ganglion in humans leads to an increase in the CGRP plasma level and causes reddening of the face ([4]: P.J. Goadsby et al., Annals of Neurology, Vol. 23, No. 2, 1988, 193-196,).

To demonstrate that hot flushes can be successfully treated using CGRP antagonists, an increased release of endogenous CGRP was induced in marmosets by stimulating the trigeminal ganglion, leading to increased blood flow through the blood vessels of the skin. The efficacy of the following test substances was characterised by determining the dose administered i.v. which reduces by 50% the increased blood flow through the skin of the face which has been brought about by endogenous CGRP:

(1) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(2) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(3,4-diethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-amide,

(3) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

(4) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(5) (*S*)-2-(4-amino-3,5-bis-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(6) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(7) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

(8) sumatriptan and

(9) zolmitriptan.

Description of method:

Marmosets of both sexes (300-400 g) are anaesthetised with pentobarbital (initially with 30 mg/kg, i.p., followed by infusion of 6mg/kg/h, i.m.). The body temperature is maintained at 37°C using a heating die base. Pancurmium is administered as a muscle relaxant (initially 1 mg/kg, 0.5 mg after each hour thereafter). The animal's head is secured in a stereotactical apparatus. After the skin on the head has been opened using a lengthwise incision, a small hole is drilled in the skull and a bipolar electrode (Rhodes SNES 100) is lowered into the trigeminal ganglion.

Locating the ganglion is made easier by the use of an X-ray which shows up the bone structure of the skull. The petrous bone serves as a guide for placing the electrode (CCX-Digital X-ray apparatus). The position of the electrode in the ganglion is monitored at the end of each experiment. The stimulation parameters are:
10 Hz, 2 mA, 2 msec, for 30 sec.

The blood flow in the micro-vessels of the facial skin is determined by laser Doppler flow measurement using a PeriFlux Laser Doppler System.
The animals are exposed to 2 to 3 stimulation periods at intervals of 30 minutes in each case. The first stimulation serves as a reference value for the other stimulations. The test substances are administered i.v. 5 minutes before the 2nd and 3rd stimulation periods.

The Examples which follow describe pharmaceutical preparations which contain as active substance a selected CGRP antagonist according to the present invention for use according to the invention, a physiologically acceptable salt thereof or a hydrate of the salt. In the following table, the mentioned CGRP antagonists are numbered for identification of active ingredients in the tables of the examples.

Active ingredients

Subst. No.	Substance
1	CGRP-Antagonist (1) or a physiologically acceptable salt thereof or a hydrate of said salt [1a]

Subst. No.	Substance
2	CGRP-Antagonist (2) a physiologically acceptable salt thereof or a hydrate of said salt [2a]
3	CGRP-Antagonist (3) a physiologically acceptable salt thereof or a hydrate of said salt [3a]
4	CGRP-Antagonist (4) a physiologically acceptable salt thereof or a hydrate of said salt [4a]
5	CGRP-Antagonist (5) a physiologically acceptable salt thereof or a hydrate of said salt [5a]
6	CGRP-Antagonist (6) a physiologically acceptable salt thereof or a hydrate of said salt [6a]
7	CGRP-Antagonist (7) a physiologically acceptable salt thereof or a hydrate of said salt [7a]
8	CGRP-Antagonist (8) a physiologically acceptable salt thereof or a hydrate of said salt [8a]
9	CGRP-Antagonist (9) a physiologically acceptable salt thereof or a hydrate of said salt [9a]
10	CGRP-Antagonist (10) a physiologically acceptable salt thereof or a hydrate of said salt [10a]
11	CGRP-Antagonist (11) a physiologically acceptable salt thereof or a hydrate of said salt [11a]
12	CGRP-Antagonist (12) a physiologically acceptable salt thereof or a hydrate of said salt [12a]
13	CGRP-Antagonist (13) a physiologically acceptable salt thereof or a hydrate of said salt [13a]
14	CGRP-Antagonist (14) a physiologically acceptable salt thereof or a hydrate of said salt [14a]
15	CGRP-Antagonist (15) a physiologically acceptable salt thereof or a hydrate of said salt [15a]
16	CGRP-Antagonist (16) a physiologically acceptable salt thereof or a hydrate of said salt [16a]

Subst. No.	Substance
17	CGRP-Antagonist (17) a physiologically acceptable salt thereof or a hydrate of said salt [17a]
18	CGRP-Antagonist (18) a physiologically acceptable salt thereof or a hydrate of said salt [18a]
19	CGRP-Antagonist (19) a physiologically acceptable salt thereof or a hydrate of said salt [19a]
20	CGRP-Antagonist (20) a physiologically acceptable salt thereof or a hydrate of said salt [20a]
21	CGRP-Antagonist (21) a physiologically acceptable salt thereof or a hydrate of said salt [21a]
22	CGRP-Antagonist (22) a physiologically acceptable salt thereof or a hydrate of said salt [22a]

Example 1a

Tablets for 100 mg CGRP-antagonist

Composition/tablet:

CGRP-antagonist	100 mg
Lactose	375 mg
Magnesiumstearate	3.0 mg
Povidone	8.5 mg
Crospovidone	14.4 mg

Volatile component: water

Method of preparation:

CGRP-antagonist and Lactose (fine) are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with an aqueous solution of Povidone. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute

with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Crospovidone for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 1b

Tablets for 10 mg CGRP-antagonist

Composition/tablet:	
CGRP-antagonist	10.0 mg
Lactose	475 mg
Magnesiumstearate	3.0 mg
Povidone	8.5 mg
Crospovidone	14.4 mg
Volatile component: water	

Method of preparation:

CGRP-antagonist and Lactose (fine) are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with an aqueous solution of Povidone. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Crospovidone for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 1c

Tablets for 600 mg CGRP-antagonist

Composition/Tablet:	
CGRP-antagonist	600 mg

Lactose	175 mg
Magnesiumstearate	6 mg
Povidone	17 mg
Crospovidone	28.8 mg

Volatile component: water

Method of preparation:

CGRP-antagonist and Lactose (fine) are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with an aqueous solution of Povidone; The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Crospovidone for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 1d

Tablets for 100 mg CGRP-antagonist

Composition/Tablet:

CGRP-antagonist	100 mg
Lactose	403 mg
Magnesiumstearate	3.1 mg
Povidone	9.1 mg
Crospovidone	15.3 mg

Volatile component: water

Method of preparation:

CGRP-antagonist and Lactose (fine) are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with an aqueous solution of Povidone. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute

with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Crospovidone for five minutes and afterwards with magnesiumstearate for one minute. The finished composition is pressed in a tablet press with an adequate diameter.

The described methods of preparation are the basic principle of further examples shown in the following table.

In the examples 10-600 mg CGRP-antagonist as active form, as a physiologically acceptable salt thereof or a hydrate of said salt is used.

Table of Example 1a-d

Expl.	Substance No.	mg	mg Lactose	mg Povidone	mg Crospovidone	mg Magnesium-stearate	∅ [mm]
1.1	3	40	80.0	1.8	3.0	0.6	7
1.2	6a	100	200.0	4.5	7.6	1.6	9
1.3	11a	70	140.0	3.2	5.3	1.1	8
1.4	2	180	360.0	8.1	13.7	2.8	12
1.5	6	120	240.0	5.4	9.1	1.9	10
1.6	3	10	70.0	1.2	2.0	0.4	6
1.7	17	270	540.0	12.2	20.6	4.2	13
1.8	3a	220	440.0	9.9	16.7	3.4	13
1.9	14	140	280.0	6.3	10.7	2.2	11
1.10	5	230	460.0	10.4	17.5	3.6	13
1.11	1	230	460.0	10.4	17.5	3.6	13
1.12	16	40	80.0	1.8	3.0	0.6	7
1.13	3	80	160.0	3.6	6.1	1.2	9
1.14	4a	320	540.0	12.9	21.8	4.5	13
1.15	13	340	580.0	13.8	23.3	4.8	13
1.16	21	170	340.0	7.7	12.9	2.7	12
1.17	1a	110	220.0	5.0	8.4	1.7	11
1.18	5	170	340.0	7.7	12.9	2.7	12
1.19	5a	320	540.0	12.9	21.8	4.5	13
1.20	4	30	60.0	1.4	2.3	0.5	6
1.21	2a	600	600.0	18.0	30.5	6.2	13
1.22	15	300	600.0	13.5	22.8	4.7	13
1.23	7	160	320.0	7.2	12.2	2.5	12
1.24	7a	160	320.0	7.2	12.2	2.5	12
1.25	4	170	340.0	7.7	12.9	2.7	12

Example 2a

Tablets for 100 mg CGRP-antagonist

Composition:

CGRP-antagonist	100 mg
Lactose	284 mg
Microcrystalline cellulose	95 mg
Magnesiumstearate	7.2 mg
Croscarmellose	7.3 mg
Volatile component: water	

Method of preparation:

CGRP-antagonist, Lactose (fine) and microcrystalline cellulose are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with water. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Croscarmellose for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 2b

Tablets for 10 mg CGRP-antagonist

Composition:

CGRP-antagonist	10.0 mg
Lactose	274 mg
Microcrystalline Cellulose	109.5 mg
Magnesiumstearate	7.2 mg
Croscarmellose	7.3 mg
Volatile component: water	

Method of preparation:

CGRP-antagonist, Lactose (fine) and microcrystalline cellulose are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with Water. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Croscarmellose for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 2c

Tablets for 400 mg CGRP-antagonist

Composition:

CGRP-antagonist	400 mg
Lactose	194 mg
Microcrystalline cellulose	95 mg
Magnesiumstearate	7.2 mg
Croscarmellose	7.3 mg

Volatile component: water

Method of preparation:

CGRP-antagonist, Lactose (fine) and microcrystalline cellulose are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with Water. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Croscarmellose for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

Example 2d

Tablets for 100 mg CGRP-antagonist

Composition:

CGRP-antagonist	100	mg
Lactose	403	mg
Microcrystalline Cellulose	12.1	mg
Magnesiumstearate	9.3	mg
Croscarmellose	9.4	mg

Volatile component: water

Method of preparation:

CGRP-antagonist, Lactose (fine) and microcrystalline cellulose are mixed homogenously in an adequate mixer (e.g. Diosna P2); afterwards the compound is granulated with Water. The granulate material is screened with a Kressner sieve (1.6 mm) and dried for 2 h at 40°C. After that, the granulate material is sieved at 3000 U/minute with a mesh size of 1.1 mm in an adequate mill (e.g. Comill). Thereupon the granulate material is first mixed with Croscarmellose for five minutes and afterwards with magnesiumstearate for one minute. The finished composition are pressed in a tablet press with an adequate diameter.

These methods of preparation are the basic principle of further examples being shown in the following table.

In the examples 10-600 mg CGRP-antagonist as active form, as a physiologically acceptable salt thereof or a hydrate of said salt is used.

Table of Example 2a-d

Example	Substanz No.	mg	mg Lactose	mg mikrokrist. Cellulose	mg Mg-stearate	mg Cros-carmellose	∅ [mm]
2.1	5	130	195.0		5.0	5.0	10
2.2	4a	380	570.0	190.0	14.5	14.8	13
2.3	16	150	225.0	75.0	5.7	5.8	10
2.4	6a	240	360.0	120.0	9.2	9.3	12
2.5	6	30	45.0	15.0	1.1	1.2	6
2.6	3	600	400.0	200.0	15.3	15.5	13
2.7	2a	220	330.0	110.0	8.4	8.5	12
2.8	22	30	45.0	15.0	1.1	1.2	6
2.9	4	120	180.0	60.0	4.6	4.7	9
2.10	2	40	60.0	20.0	1.5	1.6	6
2.11	1	110	165.0	55.0	4.2	4.3	9
2.12	5a	180	270.0	90.0	6.9	7.0	12
2.13	6	310	465.0	155.0	11.9	12.0	13
2.14	1	390	585.0	195.0	14.9	15.1	13
2.15	1a	10	150.0	32.0	2.4	2.5	8
2.16	15	240	360.0	120.0	9.2	9.3	13
2.17	7	50	75.0	25.0	1.9	1.9	7
2.18	3	90	135.0	45.0	3.4	3.5	8
2.19	17a	190	285.0	95.0	7.3	7.4	12
2.20	6	360	540.0	180.0	13.8	14.0	13

Example 3a

Aqueous solution for nasal administration of 20% CGRP-antagonist

Composition:

CGRP-antagonist	20 mg
Mannitol	5 mg
Water	ad 0.1 ml

Method of preparation:

The active ingredient are dissolved/suspended by stirring and if necessary by heating. After mannitol is added the solution is filled up to the final volume.

Example 3b

Aqueous solution for nasal administration of 2% CGRP-antagonist

Composition:

CGRP-antagonist	2 mg
Mannitol	5 mg
Water	ad 0.1 ml

Method of preparation:

The active ingredient is dissolved/suspended by stirring and if necessary by heating. After mannitol is added the solution is filled up to the final volume.

Example 3c

Aqueous solution for nasal administration of 40% CGRP-antagonist

Composition:

CGRP-antagonist	40 mg
Mannitol	5 mg
Water	ad 0.1 ml

Method of preparation:

The active ingredient is dissolved/suspended by stirring and if necessary by heating. After mannitol is added the solution is filled up to the final volume.

Example 3d

Aqueous solution for nasal administration of 20% CGRP-antagonist and 1.5% Labrasol

Composition:

CGRP-antagonist	20 mg

Labrasol	1.5 mg
Mannitol	5 mg
Water	ad 0.1 ml

Method of preparation:
The active ingredient is dissolved/suspended by stirring and if necessary by heating. After mannitol and labrasol are added the solution is filled up to the final volume.

Example 3e

Aqueous solution for nasal administration of 50% CGRP-antagonist and 1.5% Labrasol

Composition:

CGRP-antagonist	50 mg
Rizatriptan	2 mg
Labrasol	1.5 mg
Mannitol	5 mg
Wasser	ad 0.1 ml

Method of preparation:
The active ingredient is dissolved/suspended by stirring and if necessary by heating. After mannitol and labrasol are added the solution is filled up to the final volume.

This method of preparation is the basic principle of further examples being shown in the following table.

Table of Example 3a-e

Example	CGRP-Antagonist No.	mg	mg Mannitol	mg Labrasol
3.1	3	20	5	3.00
3.2	2	10	5	1.50
3.3	11a	10	5	3.00

Example	CGRP-Antagonist No.	mg	mg Mannitol	mg Labrasol
3.5	6	10	5	0.00
3.6	13	5	5	1.50
3.7	4a	10	5	3.00
3.8	3a	5	5	3.00
3.9	3	20	5	3.00
3.10	1	5	5	0.00
3.11	4	10	5	1.50
3.12	12	10	5	3.00
3.13	4	20	5	3.00
3.14	22	5	5	0.00
3.15	14a	20	5	0.00

Pellets

Pharmaceutical preparations of CGRP antagonist according to the present invention in form of small particles e.g pellets are also possible. At this the active ingredient is sprayed on neutral starter cores made of saccharose and starch or made of microcrystalline cellulose.

In the case of pH dependent solubility of the active ingredient, alkaline starter cores are used.

The method of preparation includes following steps:

1. Choice / method of preparation of starter cores
2. Spraying of the active ingredient layer

For improvement of stability or flavour or for sustained release the last facultative step is coating of the pellets

Example 4a

Method of preparation of alkaline starter cores:

Composition:

Povidone K25	3 weight parts
Microcrystalline cellulose	20 weight parts
Meglumine	77 weight parts

77 Weight parts meglumine, 20 weight parts microcrystalline cellulose and 3 weight parts Povidone K25 are mixed in an adequate mixer for 15 minutes. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h by metered addition of water. The moment of torsion of 19% is controlled by the proportioning of the water. The diameter of the holes of the die base at the end of the extruder is 0.8 mm.

The spheronizing of the product is made by a spheronizer, for 3 minutes at approx. 850 RPM.

Drying of the pellets at 80°C for 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieve die bases (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used in the following processes.

Example 4b

Method of spraying of 100 mg CGRP-antagonist

Composition:

Starter cores	200 weight parts
Hydroxypropylcellulose	38 weight parts
Talcum	20 weight parts
CGRP-antagonist	100 weight parts

Hydroxypropylcellulose is solved by stirring in 250 weight parts of 2-propanol. Subsequently the active ingredient and talcum are dispersed in this solution by stirring.

200 weight parts of starter cores are sprayed with the above described dispersion in a fluid bed dryer at an incoming air temperature of 20°C to 30°C. The pellets are afterwards dried in a drying chamber with circulating air for 8 h at 35°C.

To remove of agglomerated pellets the pellets are sieved through a sieve with a mesh number of 1.25 mm.

Example 4c

Method of spraying of 10 weight parts CGRP-antagonist

Composition:

Starter cores	100 weight parts
Hydroxypropylcellulose	24 weight parts
Talcum	12 weight parts
CGRP-antagonist	10 weight parts

Hydroxypropylcellulose is solved by stirring in 250 weight parts of 2-propanol. Subsequently the active ingredient and talcum are dispersed in this solution by stirring.

100 weight parts of starter cores are sprayed with the above described dispersion in a fluid bed dryer at an incoming air temperature of 20°C to 30°C. The pellets are afterwards dried in a drying chamber with circulating air for 8 h at 35°C.

To remove of agglomerated pellets the pellets are sieved through a sieve with a mesh size of 1.25 mm.

Example 4d

Method of spraying of 400 weight parts CGRP-antagonist

Composition:

Starter cores	100 weight parts
Hydroxypropylcellulose	62 weight parts
Talcum	24 weight parts
CGRP-antagonist	400 weight parts

Hydroxypropylcellulose is solved by stirring in 250 weight parts of 2-propanol. Subsequently the active ingredient and talcum are dispersed in this solution by stirring.

100 weight parts of starter cores are sprayed with the above described dispersion in a fluid bed dryer at an incoming air temperature of 20°C to 30°C. The pellets are afterwards dried in a drying chamber with circulating air for 8 h at 35°C.

To remove of agglomerated pellets the pellets are sieved through a sieve with a mesh size of 1.25 mm.

In general the build up of the layer of active ingredient is always the same, but variation of the kind and the amount of active ingredient and the excipients is possible.

The following table shows different compositions of the above described method. In the examples 10-600 weight parts CGRP-antagonist as active form, as a physiologically acceptable salt thereof or a hydrate of said salt is used.

Table of Example 4b-d

Ex.	CGRP-Antagonist No.	Wp	*WP Povidone	*WP. HPC	*WP. Starterpellets	*WP. Talkum	*WP. Iso-propanol	*WP. Ethanol	*WP. Water
4.1	2	70	14.0	0.0	70.0	15.4	2630	0	0
4.2	22	240	48.0	0.0	240.0	52.8	1600	0	1600
4.3	5a	60	0.0	12.0	60.0	13.2	0	1600	0
4.4	1a	230	0.0	46.0	230.0	50.6	0	0	1770
4.5	11	40	0.0	8.0	450.0	49.8	4210	0	0
4.6	12	220	0.0	44.0	220.0	48.4	0	0	2940
4.7	4	380	76.0	0.0	380.0	83.6	3610	0	0
4.8	7	380	0.0	76.0	380.0	83.6	2230	0	0
4.9	4	230	0.0	46.0	230.0	50.6	0	1640	0
4.10	11a	360	72.0	0.0	360.0	79.2	1700	0	0
4.11	6	250	0.0	50.0	250.0	55.0	0	0	1760
4.12	4	280	0.0	56.0	280.0	61.6	0	1800	0
4.13	13	360	72.0	0.0	360.0	79.2	0	2400	0
4.14	4	120	0.0	24.0	360.0	50.4	0	0	4950
4.15	14a	310	0.0	62.0	310.0	68.2	0	0	2670
4.16	6	600	0.0	120.0	600.0	132.0	1900	0	0
4.17	2	280	56.0	0.0	280.0	61.6	2230	0	0

Ex.	CGRP-Antagonist No.	Wp	*WP Povidone	*WP. HPC	*WP. Starterpellets	*WP. Talkum	*WP. Iso-propanol	*WP. Ethanol	*WP. Water
4.18	17	350	70.0	0.0	350.0	77.0	0	1610	0
4.19	5	10	2.0	0.0	100.0	11.2	0	0	1930
4.20	3	180	0.0	36.0	180.0	39.6	1870	0	0
4.21	14	100	20.0	0.0	100.0	22.0	0	1680	0
4.22	16a	80	16.0	0.0	80.0	17.6	1900	0	0
4.23	4	20	0.0	4.0	350.0	37.4	0	0	1930
4.24	6a	300	0.0	60.0	300.0	66.0	0	2890	0
4.25	2	290	0.0	58.0	290.0	63.8	2670	0	0
4.26	22	280	56.0	0.0	280.0	61.6	1890	0	0
4.27	3a	70	14.0	0.0	70.0	15.4	0	3210	0
4.28	4a	50	0.0	10.0	50.0	11.0	0	0	2890
4.29	7a	40	8.0	0.0	140.0	18.8	2600	0	0

*WP= weight parts

Extrudates

Pharmaceutical preparations of CGRP antagonist according to the present invention in form of extrudates are also possible. After cutting/spheronizing the extrudates are filled directly into capsules or are used for tablets after grinding.

The method of preparation has following steps:

1. Extrusion
2a. cutting/spheronizing
2b. grinding and subsequently pressing to tablets

Example 5a

Method of preparation of moist extrudates

Composition:

Povidone K25	6	weight parts
Microcrystalline cellulose	40	weight parts
CGRP-antagonist	100	weight parts

119 weight parts CGRP-antagonist, 40 weight parts microcrystalline cellulose (Avicel PH 101) and 6 weight parts povidone (Kollidon K25) are mixed for 15 minutes in an

adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h by metered addition of water. The moment of torsion of 19% is controlled by the proportioning of the water. The diameter of the holes of the die base at the end of the extruder 0.8 mm.

The spheronizing of the product is made by a spheronizer, for 3 minutes at approx. 850 RPM.

Drying of the pellets at 80°C for 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieves (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

Example 5b

Method of preparation of moist extrudates

Composition:

Povidone K25	4	weight parts
Microcrystalline cellulose	30	weight parts
CGRP-antagonist	10.0	weight parts

10.0 weight parts CGRP-antagonist, 30 weight parts microcrystalline cellulose (Avicel PH 101) and 4 weight parts povidone (Kollidon K25) are mixed for 15 minutes in an adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h by metered addition of water. The moment of torsion of 19% is controlled by the proportioning of the water. The diameter of the holes of the die base at the end of the extruder is 0.8 mm.

The spheronizing of the product is made by a spheronizer, for 3 minutes at approx. 850 RPM.

Drying of the pellets at 80°C for 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieves (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

Example 5c

Method of preparation of moist extrudates

Composition:

Povidone K25	15	weight parts
microcrystalline cellulose	110	weight parts
CGRP-antagonist	400	weight parts

400 weight parts CGRP-antagonist, 110 weight parts microcrystalline cellulose (Avicel PH 101) and 15 weight parts povidone (Kollidon K25) are mixed for 15 minutes in an adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h by metered addition of water. The moment of torsion of 19% is controlled by the proportioning of the water. The diameter of the holes of the die base is 0.8 mm.

The spheronizing of the product is made by a spheronizer, for 3 minutes at approx. 850 RPM.

Drying of the pellets at 80°C for 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieve die bases (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

The following table shows different compositions of the above described method. In the examples 10-600 weight parts CGRP-antagonist as active form, as a physiologically acceptable salt thereof or a hydrate of said salt is used.

Table of Example 5a-c

Ex.	CGRP-Antagonist No.	*WP	*WP Povidone	*WP Poloxamer	Polyethylen-glycol 4000
5.1	6	80	28.0	2.7	84
5.2	1a	110	38.5	3.7	

Ex.	CGRP-Antagonist No.	*WP	*WP Povidone	*WP Poloxamer	Polyethylen-glycol 4000
5.3	14a	170	59.5	5.7	
5.4	6a	100	35.0	3.4	
5.5	5	80	28.0	2.7	
5.6	6	20	7.0	0.7	21
5.7	4a	200	70.0	6.8	210
5.8	2a	40	14.0	1.4	42
5.9	17	50	17.5	1.7	52.5
5.10	7	70	24.5	2.4	73.5
5.11	12	110	38.5	3.7	
5.12	2	600	210.0	20.3	
5.13	21	130	45.5	4.4	
5.14	5a	40	14.0	1.4	42
5.15	1	160	56.0	5.4	
5.16	3	60	21.0	2.0	63
5.17	14a	200	70.0	6.8	
5.18	6	80	28.0	2.7	84
5.19	16	150	52.5	5.1	
5.20	3	10	3.5	0.3	10.5

*WP= Weight parts

Example 6a

Method of preparation of melting extrudates

Composition:

Povidone K25	6	weight parts
Poloxamer	40	weight parts
CGRP-Antagonist	119	weight parts

100 Weight parts CGRP_Antagonist, 40 weight parts poloxamer and 6 weight parts povidone are mixed for 15 minutes in an adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h. The moment of torsion of 19% is controlled by temperature. The diameter of the holes of the die base is 0.8 mm.

The discharging extrudate are cutted and spheronized with an adequate spheronizer for 3 minutes at 40°.
Drying of the pellets at 80°C for approx. 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieve die bases (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

Example 6b

Method of preparation of melting extrudates

Composition:		
Povidone K25	2	weight parts
Poloxamer	30	weight parts
CGRP-antagonist	10	weight parts

10 Weight parts CGRP-antagonist, 30 weight parts poloxamer and 2 weight parts povidone are mixed for 15 minutes in an adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h. The moment of torsion of 19% is controlled by temperature. The diameter of the holes of the die base is 0.8 mm.
The discharging extrudate are cutted and spheronized with an adequate spheronizer for 3 minutes at 40°.
Drying of the pellets at 80°C for approx. 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieve die bases (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

Example 6c

Method of preparation of melting extrudates

Composition:

Povidone K25	18	weight parts
Poloxamer	132	weight parts
CGRP-antagonist	400	weight parts

400Weight parts CGRP-antagonist, 132 weight parts poloxamer and 18 weight parts povidone are mixed for 15 minutes in an adequate mixer. Afterwards the composition is extruded through a twin screw extruder at a rate of 1 kg/h. The moment of torsion of 19% is controlled by temperature. The diameter of the holes of the die base is 0.8 mm.

The discharging extrudate are cutted and spheronized with an adequate spheronizer for 3 minutes at 40°C.

Drying of the pellets at 80°C for approx. 1.5 h in a fluid bed dryer.

The material is screened by a tumble screener with different sieve die bases (0.71-1.25 mm). The adequate fractions between 0.71 and 0.90 resp. 0.90 and 1.12 mm are used.

The following table shows different compositions of the above described method. In the examples 10-600 weight parts CGRP-antagonist as active form, as a physiologically acceptable salt thereof or a hydrate of said salt is used.

Table of Example 6a-c

Ex.	CGRP-Antagonist No.	*WP	*WP Povidone	*WP Poloxamer	Polyethylen-glycol 4000
6.1	17a	120	6.0	31.5	
6.2	7	130	6.5	34.1	
6.3	2a	90	4.5	23.6	70.88
6.4	3a	40	2.0	10.5	31.50
6.5	16a	30	1.5	7.9	23.63
6.6	2	20	1.0	5.3	15.75
6.7	16	110	5.5	28.9	
6.8	5a	180	9.0	47.3	
6.9	21a	150	7.5	39.4	
6.1	3	90	4.5	23.6	

Ex.	CGRP-Antagonist No.	*WP	*WP Povidone	*WP Poloxamer	Polyethylen-glycol 4000
6.11	16	190	9.5	49.9	
6.12	13	600	30.0	157.5	
6.13	5	130	6.5	34.1	
6.14	15	150	7.5	39.4	
6.15	1	130	6.5	34.1	
6.16	4a	110	5.5	28.9	86.63
6.17	4	180	9.0	47.3	
6.18	5	90	4.5	23.6	
6.19	17	150	7.5	39.4	
6.20	4	100	5.0	26.3	
6.21	1a	70	3.5	18.4	55.13
6.22	13	20	1.0	5.3	15.75
6.23	4	200	10.0	52.5	
6.24	13	10	0.5	2.6	7.88
6.25	2	30	1.5	7.9	23.63

*WP= Weight parts

Example 7

Subsequent treatment: production of tablets

The extrudates are grinded in an adequate mill. The product are used fort the production of tablets (see Example 1 and 2).

Powder inhalant

Preparation of spherically nanostructured microparticles of the active substances for manufacture of a powder inhalant

For the preparation of a solution of 4% by weight the active substance is solved in an ethanol/water (4:1)-mixture and the solution is sprayed in a way resulting a spray mist with a droplet size of the characteristic value X50 (median value = particle size/droplet size, below which 50% of the quantity of particles are found, with regard to the volume distribution of the individual particles/droplets) in the range between 1.5 and $Q_{(5.8)}$ (corresponding to the quantity of particles below 5.8 µm, based on the distribution by volume of the particles) between 30% and 100%. The resulting spray mist is dried using a drying gas with a inlet temperature of 100°C to 200°C and an outlet temperature of 40°C to 120°C. The volumetric flow of the spray gas of is 1

Nm^3/h to 15 Nm^3/h and a volumetric flow of the drying gas of 15 Nm^3/h to 150 Nm^3/h is used. The solid fraction remaining after the solvent has evaporated is separated off from the gas current by means of an inertia force separator (e.g. cyclone) and/or by a filter unit and collected.

Example 8

Capsules for powder inhalation with 0.5 mg CGRP-antagonist

Composition:

1 capsule for powder inhalation contains:

CGRP-antagonist	0.5 mg
Lactose	20 mg
Hard gelatine capsule	50 mg

Method of preparation:

The active ingredient in form of spherical nanostructured mircroparticle is mixed homogeneously with lactose. The mixture is subsequently filled into hard gelatine capsules.

This method of preparation is the basic principle of further examples being shown in the following table.

Table of Example 8

Example	CGRP-Antagonist (n)	mg	mg Lactose
8.1	4	30.00	80.00
8.2	12	10.00	60.00
8.3	21	20.00	70.00
8.4	6	30.00	80.00
8.5	16	25.00	75.00
8.6	1	30.00	80.00
8.7	3	20.00	70.00
8.8	21	10.00	60.00
8.9	3	20.00	70.00
8.10	11	0.30	50.30

Example	CGRP-Antagonist (n)	mg	mg Lactose
8.11	5	0.10	50.10
8.12	5	30.00	80.00
8.13	16	30.00	80.00
8.14	2	3.00	53.00
8.15	22	20.00	70.00
8.16	5	5.00	55.00
8.17	6	20.00	70.00
8.18	2	10.00	60.00
8.19	14	10.00	60.00
8.20	4	0.00	50.00
8.21	6	10.00	60.00
8.22	3	15.00	65.00
8.23	14	10.00	60.00
8.24	4	50.00	100.00
8.25	6	30.00	80.00
8.26	5	0.00	50.00
8.27	16	20.00	70.00

Example 9

Injectable solution with 0,5 mg CGRP-antagonist

Composition:

CGRP-antagonist 0.5 mg

physiological solution of NaCl

The active ingredient is solved in a physiological solution of NaCl.

The dose is variable, different doses are displayed in the following table.

The examples contain 0.2-30 mg of CGRP-antagonist as active form, in form of a physiologically acceptable salt thereof or a hydrate of said salt.

Table of Example 9

Example	CGRP-Antagonist Nr.	mg
9.1	5	0.20

Example	CGRP-Antagonist Nr.	mg
9.2	4a	14.30
9.3	16	4.40
9.4	6a	10.30
9.5	6	1.80
9.6	3	1.30
9.7	2a	4.40
9.8	12	9.40
9.9	4	2.60
9.10	12	8.20
9.11	21	4.30
9.12	5a	25.50
9.13	6	14.20
9.14	11	13.40
9.15	1a	5.40
9.16	15	6.90

Example 10

Suppositories with 200 mg CGRP-antagonist

Composition:

CGRP-antagonist	238 mg
Hard fat	ad 2 g

Method of preparation:

The active substance is previously ground and sieved through a suitable sieve and hard fat is added. When prepared by moulding, the medicated mass, sufficiently liquified by heating, is poured into suitable moulds. The suppository solidifies on cooling.

The dose is variable, therefore different doses are displayed in the following table.

The examples contain 50-600 mg of CGRP-antagonist as active form, in form of a physiologically acceptable salt thereof or a hydrate of said salt.

Table of Example 10

Example	CGRP-Antagonist Nr.	mg
1.1	13	250
1.2	6a	150
1.3	1a	460
1.4	12	540
1.5	6	320
1.6	3	180
1.7	17	150
1.8	3a	480
1.9	4	600
1.10	5	180

Patent Claims

1. A method of treatment or prevention of hot flushes in men who underwent castration comprising administration of an effective amount of CGRP antagonist selected from the group consisting of

(1) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(2) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(3,4-diethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-amide,

(3) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

(4) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(5) ((*S*)-2-(4-amino-3,5-bis-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(6) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(7) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

the physiologically acceptable salts thereof and the hydrates of the salts to a person in need of such treatment.

2. The method of claim 1, characterised in that it is effected as a monotherapy with a single active substance.

3. The method of claim 1, characterised in that it is effected as a supplement to conventional therapy.

4. Use of a CGRP antagonist selected from the group consisting of

(1) (*S*)-2-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(2) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(3,4-diethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-amide,

(3) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

(4) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3-chloro-5-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(5) ((*S*)-2-(4-amino-3,5-bis-trifluoromethyl-benzyl)-1-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-4-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidin-1-yl]-butane-1,4-dione,

(6) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid {(*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl}-amide,

(7) 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylic acid (*R*)-1-(4-amino-3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl ester,

the physiologically acceptable salts thereof and the hydrates of the salts for the preparation of a pharmaceutical composition for treatment or prevention of hot flushes in men who underwent castration.

5. Use according to claim 4, characterised in that the pharmaceutical composition contains only one active substance.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/013974

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/517

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037810 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; RUDOLF, KLAUS; MUELLER, STE) 6 May 2004 (2004-05-06) page 1, paragraph 1 structures 16, 117, 121 page 92 page 93, paragraph 2	1-5
X	WO 2004/037811 A (BOEHRINGER INGELHEIM; RUDOLF, KLAUS; MUELLER, STEPHAN, GEORG; STENKAMP) 6 May 2004 (2004-05-06) page 1, paragraph 1 structure 1 page 80, last paragraph - page 81, paragraph 1 page 81, paragraph 3	1-5

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2006	01/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bendl, E

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	SPETZ A-C E ET AL: "HOT FLUSHES IN MEN: PREVALENCE AND POSSIBLE MECHANISMS" JOURNAL OF THE BRITISH MENOPAUSE SOCIETY, BRITISH MENOPAUSE SOCIETY, MARLOW, GB, vol. 8, no. 2, June 2002 (2002-06), pages 57-62, XP009026297 ISSN: 1362-1807 abstract	1-5
Y	SPETZ A-C ET AL: "MOMENTARY INCREASE IN PLASMA CALCITONIN GENE-RELATED PEPTIDE IS INVOLVED IN HOT FLASHES IN MEN TREATED WITH CASTRATION FOR CARCINOMA OF THE PROSTATE" JOURNAL OF UROLOGY, BALTIMORE, MD, US, vol. 166, no. 5, November 2001 (2001-11), pages 1720-1723, XP009039446 ISSN: 0022-5347 abstract	1-5
Y	SPETZ A-C ET AL: "Hot flushes and prostate cancer: Pathogenesis and treatment" BJU INTERNATIONAL, BLACKWELL SCIENCE, OXFORD, GB, vol. 90, no. 4, September 2002 (2002-09), page 476, XP002305048 ISSN: 1464-4096 the whole document	1-5

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/013974

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] *The additional search fees were accompanied by the applicant's protest.*

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
[redacted]/EP2005/013974

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